UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/023,748 | 12/21/2001 | Oluwole T. Aloba | 2911.600 | 5061 |

5514 7590 07/15/2003

FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

| EXAMINER | |
|---|---|
| HUI, SAN MING R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | 8 |

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 10/023,748 | Applicant(s) ALOBA ET AL. | |
|---|---|---|---|
| | Examiner San-ming Hui | Art Unit 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *12-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicant's election of the invention of Group I, claims 1-11, in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The request for rejoining the invention of Groups II and III if the invention of Group I is found allowable is acknowledged. Such request will be considered carefully upon the allowance of the invention of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claims 1-11 have been examined herein to the extent they read on the elected invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the medication disclosed in page 7, line 25 to page 8, line 2, does not reasonably provide enablement for other medicament. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with

these claims. In the instant case, the specification fails to disclose information to one of skilled in the art to practice the instant invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define the "additional medicament". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "additional medicament" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the full scope of compounds required. Some compounds may not be compatible with estradiol acetate (an estrogenic agent), for example, estrogen antagonists such as tamoxifen. There is no guidance provided in the instant

specification to select the suitable additional medicament for the instant invention. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "additional medicament(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "17β-estradiol-3-lower alkanoate" recited in the claims renders the claims indefinite. It is unclear what alkanoate in the 3- position of 17β-estradiol are encompassed by the claims. Is C1-C4 alkanoate or C1-C6 alkanoate considered lower alkanoate? The instant specification merely lists the preferred "17β-estradiol-3-lower alkanoate" as 17β-estradiol-3-acetate in, for example, page 5, lines7-10, 25-29; page 6, line 4-5, 11-13, 28-31; page 8, line 10, 16-17; page 10, line 29-30. However, no clear definition was disclosed in the instant specification and thus, the metes and bounds of the claims are not clearly defined.

The expression "additional medicament" in claim 7 renders the claim indefinite because it is unclear what active agent would be considered as by the term "additional

medicament". Is the estrogen antagonist such as tamoxifen considered as the additional medicament?

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070).

Stein teaches a unit dose composition containing estradiol 3-position derivatives including estradiol-3-acetate (See col. 2, lines 9-25; particular the compound of Formula I; also col. 8, lines 6-27, Example 3). Stein also teaches estradiol-3-acetate as useful in treating menopausal syndrome (See col. 6, line 58-65). Stein also teaches the estradiol derivative composition may be formulated into oral dosage form such as tablets, or capsules (See col. 6, line 22). Stein also teaches various conventional carriers, such as suspending agents, and lubricants, can be incorporated into the composition (See col. 6, line 28-29).

Stein does not expressly teach the composition containing estradiol-3-acetate specifically.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate estradiol-3-acetate into the unit dose composition of Stein.

One of ordinary skill in the art would have been motivated to incorporate estradiol-3-acetate into the unit dose composition of Stein. It is known that estradiol 3-position derivatives can be formulated into oral unit dose composition such as tablet and capsule. Formulating any known estradiol 3-position derivatives, such as estradiol-3-acetate, into an oral dosage form such as tablet or capsule for the treatment of menopausal syndrome would have been reasonably expected to be useful.

Claims 4 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070) as applied to claims 1-3, 5, and 10-11 above, and further in view of Remington (Remington: The Science and Practice of Pharmacy, 19th ed., 1995, pages 1413, 1623-1626) and Wolfe et al. (Journal of Lipid Research, 2000;41:368-375).

Stein suggests estradiol-3-acetate oral unit tablet or capsule composition.

Stein does not expressly teach the moisture content of the composition as less than or equal to 8%. Stein does not expressly teach the employment of an inhibitor of hydrolysis. Stein does not expressly teach the additional medicament such as progestational agent is incorporated into the unit dose composition. Stein does not expressly teach the dosage unit is prepared by granulation method.

Remington teaches that silica gel (colloidal silicon dioxide), a well-known pharmaceutical ingredient, is used as tablet moisture adsorber, glidant and as suspending agent (See page 1413, col. 2). Remington also teaches that various granulation methods are well-known in the art in tablet preparation (See page 1623-1626).

Wolfe et al. teaches that the combination of estrogen and medroxyprogesterone is useful as hormonal replacement therapy, which has the benefits of reducing the VLDL and triglyceride levels (See page 374, col. 1, last paragraph to col. 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an inhibitor of hydrolysis and a secondary agent, such as progestational agent to the composition of Stein. It would have been obvious to one of ordinary skill in the art at the time the invention was made to keep the moisture content as below 8%. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition through the process of granulation.

One of ordinary skill in the art would have been motivated to incorporate an inhibitor of hydrolysis and a secondary agent, such as progestational agent to the composition of Stein. Silica gel is known to be useful as tablet moisture adsorber. Hydrolysis is a process of decomposition of a substance in the presence of water. Therefore, as the moisture content of the tablet reduce, the hydrolysis will be less likely to be carried out. Incorporating silica gel, a well known glidants and suspending agents, into the composition of Stein would have been considered as obvious to one of ordinary

skill in the art. Moreover, using silica gel to keep the moisture content to be less than 8% would be considered obvious as being within the purview of skilled artisan, absent evidence to the contrary. Furthermore, based on Wolfe, it is known that the combination of estrogen and medroxyprogesterone, progestational agent, are useful in treating menopausal syndrome. Therefore, incorporating a progestational agent to an estradiol composition would have been reasonably expected to be useful in hormonal replacement therapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617
July 14, 2003